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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,428	08/01/2003	David Bebbington	VPI/00-130-03 CON US	4377

7590 02/13/2006

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EXAMINER	
JOHNSEN, JASON H	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,428	BEBBINGTON ET AL.	
	Examiner	Art Unit	
	Jason H. Johnsen	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *8* is/are allowed.

6)☐ Claim(s) *1-11,15-22,27 and 28* is/are rejected.

7)☐ Claim(s) *12-14 and 23-26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *N/A* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/01/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 08/01/03 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner is considering the information disclosure statement.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, and 15-18, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-40 of copending Application No. 10464430. Although the conflicting claims are not identical, they are not patentably distinct from each other because several compounds embraced by Application No. 1046430 are species of the generic compounds and compositions taught by formula IIIa in the

instant application. The invention set forth in Claim 34 of said co-pending application falls entirely within the scope of claim 1-7 or, in other words, claims 1-7 are anticipated by claims 34-38 of said co-pending application. Additionally, several compounds of claim 8 of instant application are species of generic claim 24 or overlap with compounds of claim 38 of co-pending application (See claim 38, compound 20 and example IIIa-50 of instant application depicting a compound in claim 8). Claims 9 and 10 teach a composition with an additional therapeutic agent. Co-pending application's claims 40 and 41 teach the same composition. Also, claims 15-18 of the instant application are drawn to compositions used in treating Auorora-2 mediated diseases. Said co-pending application is also drawn to treating Aurora-2 mediated diseases using overlapping compounds or compositions as described in claim 47 and 51-53.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

1. Claim 11 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The intended use of a composition, i.e. "formulated for administration to a human," does not change the chemical identity of the compound or composition and is therefore, not seen to further limit the compound or composition. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

2. Claims 12, 13, 14, 23, 24, 25, and 26 are objected to for depending from a rejected base claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-3, 6, and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. All claims that include the limitation of "**substituted**", as in "optionally substituted group selected from...," "optionally substituted C_{1-6} aliphatic," "substituted or unsubstituted...," and "optionally substituted benzo ring" are indefinite. In the absence of the identity of moieties which are intended to provide substitution and thus modify the instantly claimed chemical core, the identity of the "substituted" moieties applicant intends as the invention would be difficult to ascertain. In the absence of said moieties, the claims containing the term "substituted" are not described sufficiently to distinctly point out that which applicant intends as the invention. Applicants should include the moieties which are intended to effectuate substitution into the claims wherein said moieties are supported in the specification as originally filed.

2. Claims 4, 5, 9, 10, and 11 are rejected under 35 U.S.C. 112, second paragraph, because claims that depend from an indefinite claim are also indefinite if they fail to obviate the reason the claim(s) from which they depend are rejected.

3. Claim 22 recites the limitation "wherein said GSK-3-mediated disease..." according to claim 20. There is insufficient antecedent basis for this limitation in the claim. Claim 20 does not recite a GSK-3-mediated disease; it only teaches inhibiting GSK-3 activity in a patient.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 19, 20, 21, 22, 27, and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling a method for treating certain types of cancer, diabetes, multiple sclerosis, and cardiomycete hypertrophy, comprising administering an effective amount of a compound of the formula presented in claim 1, does not reasonably provide enablement for baldness, schizophrenia, Parkinsons, Alzheimer's, Huntington's disease, AIDS-associated dementia, cancer broadly, or reperfusion/ischemia broadly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims without undue experimentation. Claim 15 teaches treating an "Aurora-2-mediated disease" broadly; claims 19 and 20 teach a method of inhibiting GSK-3 activity; claim 21 teaches a method of treating "a GSK-3-mediated disease" broadly; claim 22 depends from claim 20 and further teaches GSK-3-mediated disease to be selected from diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS-associated dementia, amyotrophic lateral sclerosis, MS, schizophrenia, cardiomycete hypertrophy, reperfusion/ischemia, or baldness; claim 27 teaches a method of inhibiting Src activity in a patient; claim 28 teaches a method of treating a Src-mediated diseases broadly. The specification discloses six biological examples of in vitro inhibition of protein kinases Aurora 2, GSK 3 and Src. However, applicant gives no actual

experimental data nor teaches how the art allows the skilled artisan to extrapolate inhibition of kinase inhibitors for therapeutic methods for treating diseases in patients. In addition, the specification fails to provide sufficient examples from the genus claimed as therapeutic agents effective *in vivo*, for the claimed treatments. Note that in cases involving physiological activity, "the scope of enablement varies inversely with the degree of unpredictability of the factors involved." *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Since this case involves unpredictable *in vitro* and *in vivo* physiological enzyme inhibition activities, any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds. The instant application provides no such evidence.

Furthermore, the instant specification provides no direction or guidance for how to use the disclosed (and claimed) compounds since there are no guidelines for determination of dosage needed to provide the inhibitory effect and no teaching or date provided which would permit the determination of an effective amount for treating these disorders. In fact there is no data showing that any one of these compounds can even inhibit said enzyme. Therefore, in view of the breadth of the claims, the chemical nature of the invention, the unpredictability of *in vitro* and *in vivo* correlation, the lack of any working examples, and the lack of any guidance in how to use the claimed compounds and compositions to actually treat these disorders, it would require an undue amount of experimentation to use the claimed inventions.

A few examples: **Cancer** generally- there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, however these compounds have been proven to be wise spectrum. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. The treatment of cancer is highly

unpredictable due to the differing forms of cancerous cells, their location, their potential for metastases, the fact that cancer therapeutics is palliative rather than curative and that cancer treatment readily harms normal tissues (see Katzung pp. 881-882). Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

The treatment of **Alzheimer's disease** is highly unpredictable due to the limited understanding of causation and to the difficulty in treating the myriad of symptoms, including memory loss, confusion, impaired judgment, personality changes, disorientation, and loss of language skills. Always fatal, Alzheimer's disease is the most common form of irreversible dementia.

The applicant has not demonstrated sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or reference to the same in the

prior art to provide a skilled artisan with sufficient guidance to practice the instant treatment of Alzheimer's as claimed. For example, the applicant only discloses that dosages should be in a therapeutically effective amount.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 27 USPQ2d 1510 (CAFC). The disclosure does not demonstrate sufficient evidence to support the applicant's claim to the treatment of Alzheimer's disease. There are not sufficient representations in the disclosure or data from references of the prior art to provide a nexus between those examples and a method of treating Alzheimer's with the claimed compound.

In order for there to be a method of treating Alzheimer's disease generally, as claimed by the applicant, it would be necessary to show how to positively affect one or more symptoms of this complex disease of the brain. Furthermore, direction, in the form of examples, or some other disclosure should teach what a therapeutically effective dose may be. The references submitted do not provide guidance to determine therapeutically effective doses. Therefore, one of ordinary skill in the art would require a significant amount of experimentation in order to determine the effective dosage to treat or prevent the multitudes of different symptoms of Alzheimer's disease with the claimed compounds, pharmaceutical compositions in combination with other therapeutic agents (See Katzung pp. 882-884).

Disease states potentially treated by these three protein kinase inhibitors are diverse and numerous. The specification gives examples of potentially treated diseases of the GSK-3 protein

kinase to include various CNS disorders such as Alzheimer's, Parkinson's, MS, Schizophrenia, and Huntington's disease. Aurora-2 has been implicated in various cancers. Src-mediated diseases include Alzheimer's and other neurodegenerative diseases. Applicant has not shown, nor is there seen in the art, a sufficient nexus between the inhibition of protein kinases and treatment of the diseases potentially mediated by these protein kinases. Inhibiting these protein kinases are not indicative/correlative to treating cancer broadly, Alzheimer's, Parkinson's MS, schizophrenia, or various other CNS disorders and neurodegenerative disorders broadly. The art does not support a direct correlation between the inhibition of Aurora-2 protein kinase, GSK-3 protein kinase or Src protein kinase and the treatment of diseases, in which the enzyme is known to be a factor.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jason H. Johnsen whose telephone number is 571-272-3106. The examiner can normally be reached on Mon-Friday, 8:30-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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